Blood Systems, Inc.

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 106 1
Rockville, MD 20852

Office of Information and Regulatory Affairs
O.M.B., New Executive Office Building
725 17th Street, N.W.
Washington, D.C. 20503

Dear Sirs:

Please find attached specific comments on:

- **Requirements of Testing Blood Donors #98N-0581**
- **Notification of Deferred Donors #98N-0607**

Blood Systems is pleased to be offered the opportunity to comment on the proposed regulations. In general, the regulations represent helpful clarification of requirements to offer safe and effective blood products.

Specific comments are included with the goal of improving clarity, maximizing blood availability or enhancing cost effectiveness.

In the case of donor notification, Blood Systems is concerned that the regulations infringe State Public Health laws and guidelines and require a public health function of the blood center. In each segment of donor notification, the regulation should take cognizance of state and local public health requirements and allow the option that notification/follow-up may be performed by an accredited public health authority.

Since the U.S. government does provide an adequate generally acceptable postal service, it is proposed that standard mail be deemed an acceptable method of communication without resort to certification of delivery since in many cases this is routinely refused or signed for by others. It is also expensive and burdensome. Acceptance of this method of notification without requiring an affirmatory response by the recipient should be acceptable unless the letter is returned as 'undeliverable'.

98N-0581

C9

The requirement for a permanent fixed address is a restrictive and burdensome obligation. What problem is being resolved by this requirement? The availability of a permanent address has no relevance to the safety, purity or potency of the product manufactured from these donors. The mobility of donors is already a major issue for recruitment and provided any needed follow up is prompt, postal notification should be acceptable. The addition of yet another reason to defer donors can only further reduce the availability of a product that is already in short supply.

Thank you for the opportunity to comment.

Sincerely,

Wm. Andrew Heaton, MD
Executive Vice President
and Chief Medical Officer

WAH:bb

Enclosures

Blood Systems, Inc.
Comments on Docket # 98N-0607
Notification of Deferred Donors

Comments on General Description

Section 5 Paragraph 3
8 weeks is allocated to complete donor notification. In situations where the confirmatory testing is sent out this may be hard to achieve in practice. This may also be a problem where research tests are used to confirm screening results for less common viruses such as HTLV.

Section 5 Paragraph 6
It is not clear why deferral of autologous donors is not required. These donors represent as much risk as homologous donors and to allow different treatment of such donors will increase the opportunity for error. It is proposed that these donors be treated similarly to homologous donors, and that donor notification be required in a fashion similar to homologous donors.

Section 5 Paragraph 7
Since the manufacturers do not believe that it is commercially viable to pursue licensing of HTLV confirmatory testing, it is proposed that the use of research tests under IND be accepted for the purpose of donor notification. In addition it is proposed that the FDA approve the use of alternate (licensed) EIA tests to confirm a single EIA test result. Two positive results by such an approach should then result in temporary donor deferral. Only a small percentage of these donors are true positives. During approximately 6 months 33,926 donors were tested for HTLV in one of our centers and 68 tested repeat reactive ,18 tested positive by the alternate EIA of which 9 (50%) confirmed positive with IFA/WB (and 3 had insufficient sample). A single positive test should not result in permanent donor deferral because of the high frequency with which these results do not confirm.

Section 5 Paragraph 10
The exclusive use of vaccinated donors to prepare specific immune globulin is opposed for the reason that the immunogens are genetically engineered with the result that the subsequent antibody may be too specific to offer adequate breadth of protection, whereas naturally acquired antibody will have a wider specificity.

Section 5 Paragraph 11
This section would require Blood Centers to notify blood donors of their STD (Syphilis) results. In many states this type of notification is the responsibility of the State Public Health Department. This may be required by state law or may represent the local standard of practice since the state has specific expertise in this area and the Blood Centers do not. It is suggested that if the notification becomes the standard that either the center or accredited state agencies be acceptable as the source of the notification.

Generally Blood Systems is opposed to the continuance of Syphilis testing because of the lack of transfusion syphilis, the fact that treponemes do not survive storage and the high incidence of aberrant results associated with mandatory notification which results in the

embarrassment of many innocent blood donors.

Section 5 Paragraph 13
Blood Systems is not opposed to referring donors to their physicians, and has provided information on the availability of alternate test centers to donors in the past. Going forward it is proposed that standard documentation provided by the State Health Department in connection with infectious disease testing be given to the donors. This may include the locations of service provision but alternatively may simply refer the donor to local healthcare institutions. To require specific referral enters the practice of medicine and is inappropriate for a blood center.

Section 5 Paragraph 14
Donor notification might include any or all of three methods- a simple letter, a return receipt letter, and a phone call to the number of record. In the State of California it is required that the EIA test result be confirmed before the donor is notified of test positivity. On occasion donors will refuse to receive registered letters routinely and a general unregistered letter will adequately convey the need for the donor to call a designated number for the purpose of telephonic notification. In addition the implication that the donor must be given (and presumably sign acknowledgement of receipt for) a deferral letter at the time of donation adds another burden and delay to a process that is already problematic enough that many do not complete the process. It is strongly recommended that medical deferral at the time of donation be considered a medical process and that a verbal explanation be considered an acceptable standard of medical practice.

Section 5 B
The requirement that donors provide proof of a permanent fixed address is burdensome and will lead to the loss of donations if those who do not have this must be deferred. In many cases donors will respond to an appeal while on vacation or may donate shortly after arriving in an area. Sometimes donors will come to donate at the workplace where they may have left their documentary identification behind. The practice in blood banking has been to accept the truthfulness in all other areas of their history and this requirement will add to the loss of donors already experienced as result of nvCJD deferral. This is potentially a major issue and comes at a time when there have been significant nationwide blood shortages.

Section 5 Paragraph 4
This section would obligate the blood center to notify the donor of the opportunity of reinstatement. Whilst this is good practice for those donors for whom there is the possibility of reinstatement, application of a blanket requirement will raise expectations in many donors that this will happen when it cannot. In addition the current FDA approved reinstatement criteria are so restrictive that these raise a sense of frustration in many donors. It would be essential that the FDA identify a complaint address so that donors who have legitimate frustration over their circumstances may communicate directly with the agency. Without some form of safety valve this obligation to discuss the issue will raise expectations that cannot be met because of regulatory obligations.

Section 6 B, C, and D
The agency significantly under-estimates the burden of the record keeping requirements

of documenting the attempts to contact the donor.

Section 7

The number of donors who are deferred as a result of health history questions averaged 13% in ABC centers in 1998. The requirement to provide documentation of the reasons at the time of donation will represent a significant cost. In addition the availability of the documentation will lead to an increase in those who contest their deferral which will necessitate further investment of expensive specialized labor which will increase cost. The estimate of 1.2% deferral is far below actuality.

Blood Systems, Inc.
Comments on Docket # 98N-0581
Donor Testing Requirements

III Introduction. The Laboratory must be CLIA Certified.

This is an appropriate change. However, it should be recognized that that this exposes the testing laboratory to additional standards. Standards that are especially relevant to the proposed change include the CLIA requirement to include "run" controls in viral marker testing, and also the staff certification/educational requirements that are not part of FDA training requirements. The run control requirement will now fall under the proposed new testing guidelines. It will also mean that laboratories that are not now inspected by the state or by the AABB will need this inspection/ accreditation. Does this imply that FDA inspectors will enforce CLIA standards?

Manufacturers must release test lots based on reference panels supplied by CBER.

This is not an unreasonable requirement. However it would be important that the sensitivity and specificity requirements are not amended without due process such that product availability is compromised.

III A. Excluding donors testing positive for anti-HBC.

The proposal calls for allowing submission of anti-HBC plasma for fractionation as well as the submission of source plasma for the same reason. While this is sound logic it would not become a requirement that this plasma be submitted as has been the practice in the past. It was expensive and burdensome to collect whole blood from donors and to be able to submit only the plasma for cost recovery.

Serologic Tests for Syphilis.

The agency is requesting comment on the validity of tests for syphilis as well as comments on the validity of these test results as markers of high risk activity. On the issue of serologic tests for syphilis, there have been no case reports of transfusion transmitted syphilis for 30 years. There are documented studies that the treponemes do not survive in stored blood at 4C, that PCR positive tremenemal DNA/RNA is not present in test positive donations and there have been no case reports of relevance to platelet transfusion. Assuming that blood products are not issued on the day of collection, this testing could be deleted.

On the issue of high risk behavior recent REDS studies have not suggested a relationship to other infectious disease markers, or to high risk behavior. At a minimum, the current regulation should be amended to allow donations that screen

positive with a treponemal test to be released for transfusion if the reagin test is negative and the donor gives a history of having been treated for syphilis with antibiotics. In the situation where the screening reagin test is positive and the confirmatory test negative the unit should similarly be released for transfusion. This test is frequently positive and a significant number of donations are lost as result of this issue. It also triggers notification obligations that result in embarrassing follow up by the health department for donors who are never truly positive.

III B Affected Products. Testing of Autologous Products.

Clearly the inclusion of autologous products under the testing requirements is a great step forward in that it has been determined that these products are occasionally transfused to the wrong patient. The exemption of these products from the testing requirements is a significant reason that registered (unlicensed) facilities (hospitals) perform collections. Since these facilities are not subject to a similar level of regulatory scrutiny as licensed facilities, they are able to provide the service for less cost than blood centers. Testing should be performed on all units and not just on the first in the series. This is good practice because it reduces the chance for mislabeling, and offers the opportunity for catching any testing errors-indeed it is the only source of information about testing error(false negatives).

HI C HTLV testing

It is helpful that the FDA proposes allowing plasma to be exempted from HTLV testing. In practice for QC reasons it will not be possible to eliminate this testing.

The shipment of untested blood for research purposes is critical for both economic and also for product development purposes.

The proposed exemption for repeat donors should be viewed in the same light as reduced testing for autologous donors. It represents a reduced, less safe standard. This is opposed.

HI D **Confirmatory Testing.**

Confirmatory testing should be performed for all donors that are initially reactive, Failure to do this denies donors of medically relevant information and represents a reduced standard of care. The additional volume of confirmatory testing will provide the manufacturers with a sales volume that will likely promote more effort to license confirmatory tests for less common viruses that are economically non-viable at present. In the case of autologous donors, this might only be performed on the first sample to reduce cost and avoid delayed release.

Blood Systems wishes to comment on the problem of donors who are initially reactive but do not confirm. With each test introduction a separate population of false positives

are eliminated as donors -in numbers that are directly proportional to their total number of donations and to the number of new tests introduced. These donors, who are repeatedly positive by an earlier generation of an EIA/screening test but negative by confirmatory testing, should be placed in a temporary deferral category such that they might be reinstated if they are negative on two occasions 6 months apart by a later, more specific/
sensitive licensed test for the same marker.

III E Testing Responsibility.

The extension of licensing standards to registered facilities is supported. It should be made clear that all blood testing facilities, whether licensed or registered should be subject to the same standards of accreditation and compliance with good manufacturing practices. This would be in line with concerns expressed by the House Energy and Commerce Oversight committee.

III F Shipment of Products for Further Use.

The FDA is proposing to approve shipment of untested product on a case by case basis. While this has been past practice, it is proposed that this might fall under "a report and proceed after 30 days if no adverse comment received" type of approval.

This section also contains statements about donor reentry. Blood Systems believes that only temporary deferral is necessary for EIA-only reactive results on two occasions six months apart. These donors are a separate group from those who are Western Blot (HIV) or RIBA (HCV) indeterminate. The FDA should allow use of alternate reentry algorithms utilizing NAT testing to resolve inconsistent results in these individuals and avoid a permanent deferral.

III G Donor Deferral.

This section contains language relating to the use of donors immunized to Hepatitis B rather than those resistant to natural strains, to be used for the manufacture of HBIG. It is at least possible that this might reduce the efficacy of the product in the situation of viral antigenic drift. This is opposed.

III J **Release panels**

No comment.

III K Alternate Procedures.

This is a critical area as a result of NAT implementation and the use of other types of unlicensed tests to assist in donor counseling.

IV B 1.Entities Affected.

It is of concern that as much as 60% of Autologous units are untested.

IV B 2. Impact assessment.

The potential cost of the impact of applying these regulations to hospitals and blood centers is underestimated.

The test marker incidence that is quoted for autologous donors is that of repeat homologous donors. The actual prevalence of HCV markers in autologous donors is, for example around 2% and sometimes higher depending on the population studied.

V Paperwork Reduction.

With the introduction of the newer computer systems and the advent of laser optical imaging, the FDA should be more aggressive addressing the potential for electronic records.

This section also contains a section on the issue of shipment of blood products for further manufacturing prior to the completion of testing.

With the advent of NAT testing it is harder to release platelet products prior to 48 hours. In situations where the product may be utilized far away from the place of manufacture, the blood centers will likely wish to ship untested product from one facility to another and utilize a common computer system for labeling purposes prior to release of the product for transfusion. These regulations should address this newly emerging requirement.

610.40 (e)2.

This section should address the need for transfer of untested product between the facilities of a single establishment licensee to allow for remote labeling.

610.40 (f) 3.

This section should allow for the use of newly developed technologies to reenter donors. This is indirectly covered by this paragraph but the referenced reentry protocols take no cogniscence of newly developed tests. This should be addressed.

610.42 Donor Deferral.

This section makes reference to a later section which allows Autologous donors to avoid deferral as a result of infectious disease testing. Blood Systems is opposed to this.

These individuals may become regular donors at a later date and should be deferred like any other donor.

610.41 (d).

Since the risk of post transfusion syphilis is diminishingly small, units that confirm negative by a specific treponemal test should be made available for transfusion.

610.41(e).

The point about donor reentry has been made earlier. The response to the proposed regulation on donor deferral Docket 98N-0607 addresses the need to promote a less restrictive approach to the donor deferred for stable false positive EIA test results that do not evolve over time.

CROSS FILE SHEET

File Number: 98N 0581/C9

See File Number: 98N-0607/C7